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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/809,425	03/26/2004	Mai Levite	LEVITE3	8418
1444 7590 07/24/2007 BROWDY AND NEIMARK, P.L.L.C. 624 NINTH STREET, NW SUITE 300 WASHINGTON, DC 20001-5303			EXAMINER JUEDES, AMY E	
			ART UNIT 1644	PAPER NUMBER
			MAIL DATE 07/24/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/809,425	LEVITE, MAI	
	Examiner	Art Unit	
	Amy E. Juedes, Ph.D.	1644	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 January 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) 1-4, 7 and 10-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5, 6, 8, 9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1644

DETAILED ACTION

1. Applicant's election of Group III, claims 5-9 and 12-16, drawn to a method of upregulating T cell activity, in the reply filed on 1/8/07 is acknowledged. Applicant has further elected the species of in-vitro as the method of administration, and neoplastic disease as the species of T cell related disease. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-4 and 10-11 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant has indicated that claims 12-14 and 16 read on the elected species. However, claim 12 is drawn to a method of upregulating T cell activity in a subject comprising administering glutamate to the subject. This clearly involves in vivo administration, while Applicant has elected in vitro administration. Even though dependent claim 14 recites that the glutamate administration is performed ex-vivo, the method is still drawn to upregulating T cell activity in a subject (i.e. an in vivo method). Therefore, Claims 7 and 12-16 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species.

Claims 5-6 and 8-9 read on the elected invention and are being acted upon.

2. The information disclosure statement, filed on 12/7/05 is acknowledged. However, reference WO 99/50393 has been lined through since it fails to comply with 37 CFR 1.98(a)(3) which requires a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each reference listed that is not in the English language.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1644

4. Claims 5-6 and 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 5-6 and 8-9 are indefinite in the recitation of "modulating" a T cell "activity". It is not clear what direction, degree, or type of "modulation" is required. For example "modulates" might encompass an increase or a decrease in activity. Additionally, modulate might indicate that an activity is turned on or off, or could also indicate an increase or decrease of a particular activity to an unspecified degree. In addition, said modulation could be intermittent, or constant. Furthermore, it is not clear what "activity" is to be modulated/upregulated. For example, are the claims intended to encompass modulating a regulatory T cell activity, such as production of TGF- β ?

B) Claims 5-6 and 8 are indefinite in the recitation of a "T cell activity modulating glutamate analog". In the absence of hyphenation, it is unclear what the claims are referring to. Are the claims intended to mean a glutamate analog that modulates T cell activity (i.e. a T-cell-activity-modulating glutamate analog)?

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 5-6 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, there is insufficient written description to demonstrate that applicant was in possession of the claimed genus of glutamate "analog".

The instant specification on page 43 states that a "glutamate analog" refers to an amino acid, amino acid derivative, or other molecule having a substantial degree of

Art Unit: 1644

structural or functional identity to glutamate. Therefore, the instant claims encompass analogs that are completely structurally unrelated to glutamate, that have a similar "functional identity". The claims under examination are drawn to glutamate analogs that upregulate a T cell activity. Thus, the claims encompass any molecule capable of upregulating any T cell activity (for example helper T cell activities, including proinflammatory cytokine production or proliferation, or even T regulatory cell activities such as secretion of TGF- β or inhibition of immune responses). Thus, the claims might encompass a broad range of structurally and functionally different analogs, including for example cytokines, costimulatory molecules, nucleic acids, antibodies, etc. that can increase any type of T cell activity. In contrast to the broad range of structurally and functionally different analogs encompassed by the claims, the instant specification only discloses related analogs that are structurally similar to glutamate (for example, AMPA, ODAP, CNQX, etc. as disclosed on pages 33 and 45 of the specification). Said related analogs are not sufficiently representative of the broad range of structurally and functionally different molecules encompassed by the claims. Thus, one of skill in the art would conclude that the specification fails to provide adequate written description to demonstrate that Applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F. 3d 1559, 43, USPQ2d 1398.

7. Claims 5-6 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method would function as a method for upregulating T cell activity as broadly claimed.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention,

Art Unit: 1644

see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

The instant claims are drawn to a method of upregulating T cell activity comprising exposing T cells to glutamate or a glutamate analog. This encompasses upregulating a wide range of activities of different types of T cells (for example activities of regulatory T cells, CD4 T cells, CD8 T cells, including activities such as proliferation, cytokine production, etc.). It is known that T cells express receptors for glutamate, and that exposure of T cells to glutamate can increase calcium release (see Lombardi et al.). However, despite increasing calcium release, glutamate decreases T cell proliferation (see Lombardi et al., Fig. 7). Thus, while glutamate might be capable of upregulating certain T cell activities, for example calcium release, the prior art teaches that glutamate does not increase all T cell activities (for example T cell proliferation), as is encompassed by the instant claims.

Thus, based on the state of the art, the instant specification must provide a sufficient and enabling disclosure commensurate in scope with the instant claims. The instant specification demonstrates that T helper cell clones treated with glutamate display increased production of cytokines and that peripheral blood T cells treated with glutamate display

Art Unit: 1644

increased chemotaxis. However, this is not commensurate in scope with the instant claims, which encompass increasing any activity of any type of T cell, not just cytokine production by T helper cells or chemotaxis of peripheral blood T cells. Thus, given the state of the art and the lack of guidance provided by the instant specification, the method as broadly claimed must be considered highly unpredictable. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 5-6 and 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Lombardi et al., 2001 (of record).

Lombardi et al. teach a method of upregulating peripheral blood lymphocyte calcium signaling (i.e. a T cell activity) comprising culturing said lymphocytes with glutamate or glutamate analogs, such as AMPA (see page 937 and 939 in particular). Since peripheral blood lymphocytes comprise T cells, Lombardi et al. have exposed or administered glutamate to T cells, as recited in the instant claims.

Thus, the reference clearly anticipates the invention.

10. Claims 5-6 and 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Frassanito et al., 2001, as evidenced by Droge et al. 1988.

Frassanito et al. teach a method increasing cytokine production from T cells from cancer patients comprising culturing the T cells in RPMI medium (see page 191-192 in particular). As evidenced by Droge et al., cell culture media such as RPMI contains glutamate (see pages 126-127). Therefore, Frassanito et al. have exposed the T cells to glutamate. Furthermore, Frassanito et al. teach culturing the T cells with anti-CD3, PHA, IL-2, anti-CD28, or IL-6 (see page 191 in particular). The instant specification on page 43 states that a "glutamate analog" refers to a molecule having a substantial

Art Unit: 1644

degree of functional identify to glutamate. Since anti-CD3, IL-2, PHA, anti-CD28, and IL-6 all upregulate T cell activity, they can be considered natural or synthetic T cell upregulating glutamate "analogs".

Thus, the reference clearly anticipates the invention.

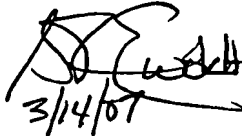
11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 8am - 5pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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3/14/07
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